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EDITORIAL REVIEW

Effects of chronic protein-calorie malnutrition on the kidney

Protein-calorie malnutrition is a widespread public health problem that contributes considerably to mortality and morbidity in areas where it is prevalent [1, 2]. A look at the world distribution of protein-calorie malnutrition indicates that the areas most affected are those countries where large proportions of the population are living under conditions of limited social and economic development [1]. The United States has considered itself one of the best-fed nations of the world. While this may be true, its attitude of self-satisfaction was challenged seriously by findings reported recently by the National Nutrition Survey [3]. Many persons, particularly among the lower income groups, were found to be malnourished. The growth of children under six years of age was below desirable standards in a number of areas. A high incidence of iron deficiency anemia was observed in infants and young children and in women during their reproductive years.

Protein-calorie malnutrition is more than a medical problem. Social, cultural and economic factors are involved. In underdeveloped countries, it results from two main factors: a diet that is quantitatively and qualitatively inadequate plus superimposed stress, usually of infectious origin [4]. A deficient diet results, in turn, from varying combinations of low food production, inadequate preservation and distribution of foods, restricted purchasing power, poor food habits and deficient knowledge of the relation between diet and health. Excessive incidence of infectious disease is a consequence of poor environmental conditions, inadequate knowledge of epidemiologic factors, poor personal hygiene and insufficient health services. These factors are interrelated and act synergistically to the detriment of nutritional status. The clinical result depends on many determinants: on the severity and duration of the nutritional deficiencies of protein and calories, on the relative importance of the deficiency of protein to that of calories, on the nature and severity of other associated nutritional deficiencies, on the age of the person affected and on the presence of other complications. The mild and moderate forms occurring in children, frequently unrecognized and misinterpreted, are primarily characterized by inadequate growth and development. In adults, malnutrition reduces weight, performance and resistance to infection [4].

Before describing the changes in renal structure and function which occur in malnourished humans or animals, it is crucial to appreciate that at this stage of our knowledge it is very difficult to determine which changes reflect a direct deleterious effect of malnutrition on the kidney and which represent an adaptation by the kidney to the nutritional insult. The former state implies a pathological change, the latter a physiologic response.

Renal function in malnutrition

While a great deal has been written regarding the consequences of renal functional disturbances on the composition of the internal environment and nutrition, much less has been published about the effect of nutritional disturbances on renal function. Investigators in the past have implied that the kidneys are substantially "normal" in malnutrition. The bases for such conclusions are certain observations about which there is no disagreement: 1) malnourished subjects produce urine that is generally free of protein, glucose and formed elements such as casts, red blood cells, etc.; and 2) the blood of these individuals does not exhibit characteristics which tend to appear in renal insufficiency–that is, the levels of blood urea nitrogen, creatinine and other materials which tend to accumulate in renal failure are not elevated [5]. Such negative evidence, however, neither proves the full normality of the kidneys nor provides a picture of the actual renal function in chronic protein malnutrition. In the literature of childhood malnutrition, on the other hand, there is frequent mention of the abnormalities of water and electrolyte metabolism which occur, and it seems likely that the kidney plays a major role in initiating and prolonging these abnormalities. Reports of studies on renal function in childhood malnutrition are scarce, though suggestive of significant functional disturbances [6–8].

For the past few years, we have studied the effects of chronic protein malnutrition on renal function in experimental animals, in children from Jamaica and in adult subjects from Colombia. This article summarizes our findings and reviews the pertinent literature in the field.

Glomerular filtration rate and renal plasma flow. Reports of the investigation of renal function by modern clearance tests are so few that Smith [9] stated in his monograph

that: "Whether or not renal function is modified by prolonged undernutrition cannot be decided from available evidence." As far as tests of renal function are concerned, it may be appropriate first to review studies dealing with dietary protein restriction produced under controlled conditions. Pullman et al [10] described experiments in which they fed normal adults "high (2.3 to 3 g protein per kg body wt), medium and low (0.1 to 0.4 g protein per kg body wt)" protein diets. Glomerular filtration rate and renal plasma flow fell when subjects were fed the low protein diet and increased with the high protein diet. Filtration fraction did not change, but the transport maximum of PAH (Tm_{PAH}) increased with a high protein diet. Nielson and Bang [11], however, also studied normal subjects fed varying amounts of protein and found that inulin and diodrast clearances were relatively unaffected by changes in the protein content of the diet. Sargent and Johnson [12] reported that when normal subjects were fed a calorie-deficient diet, irrespective of the percentage of calories from protein, fat or carbohydrate, there was a constant reduction in glomerular filtration rate as measured by the creatinine clearance.

Table 1 summarizes data for glomerular filtration rate and renal plasma flow in children and adults with protein-calorie malnutrition. Alleyne [6] found that GFR was markedly reduced in malnourished children and increased as they recovered. He found no consistent difference in inulin or PAH clearances between edematous and non-edematous malnourished children. Arroyave et al [13] found an average value for GFR of 14 ml/min/m^2 in nine malnourished children, as compared to an average value of 45 ml/min/m^2 in 17 well-nourished children. The well-nourished controls were older than the malnourished children, but the age difference alone could not explain the large difference in creatinine clearance values. Gordillo et al [8] measured inulin and PAH clearances in ten children who were at least 40% below average weight for their age. Seven of these children were well hydrated and three were severely dehydrated. In the well-hydrated malnourished children the clearance rates were about half the normal values and in the dehydrated malnourished about one-fifth of normal. Klahr et al [14, 15] demonstrated a marked decrease in both GFR and C_{PAH} in ten adults with protein malnutrition. Values for these measurements increased following protein repletion. GFR increased somewhat more during repletion leading to an increase in filtration fraction. Mollison [16] studied four subjects with malnutrition in the concentration camp of Belsen after World War II. He found normal clearances in two subjects with malnutrition but without edema, and reduced clearances in two other subjects with malnutrition and edema. In 11 adults with undernutrition, McCance [17] found an inulin clearance below 100 ml/min in only one subject. The subjects reported by McCance presumably were not as severely malnourished as the individuals studied by Klahr et al [18] or Mollison [16]. On the other hand, Srikantia and Gopalan [19] studied five cases of severe malnutrition with "protein deficiency edema" and found no decrease in GFR or renal plasma flow. These subjects differ from others reported in the literature in that they were oliguric at the time of study. It is unexplained why these subjects had normal renal plasma flow in the presence of reduced blood volume and hypotension.

It then seems that in children, protein-calorie malnutrition leads to a decrease in both renal plasma flow and glomerular filtration rate [6, 8]. In adult subjects, conflicting results on the effects of protein malnutrition on GFR and RPF have been reported [14, 17]. These differences in adults may relate to the severity and duration of the malnutrition.

Possible mechanisms responsible for the decreased GFR and RPF. The forces determining glomerular filtration rate

Table 1. Glomerular filtration rate and renal plasma flow in malnourished subjects

Investigator	Malnourished				Repleted or Normal			
	No. of subjects	C_{In}	C_{PAH} *ml/min*	FF	No. of subjects	C_{In}	C_{PAH} *ml/min*	FF
Alleyne [6]	8 children	47.1	249.4	0.21	14 children	92.4	321.2	0.29
	7 children[a]	42.9	184.0	0.27				
Arroyave et al [13]	9 children	13.7	—	—	9 children	33.9	—	—
					17 normal children	45.0		
Gordillo et al [8]	10 children	23.0	108.4		25 normal children	64.0	294	0.23
Klahr [14, 15]	10 adults	64.1	325.8	0.20	10 adults	88.3	381.1	0.24
McCance [17]	11 adults	119.4	—			—		
	11 adults	100.9	—			—		
Mollison [16]	2 adults[a]	53, 70	230, 383[b]			—		
	2 adults	124, 141	340, 710[b]			—		

[a] Edema was present in these subjects at the time of study. Mean values are given in ml/min. The data for adults are corrected for 1.73 m^2. The data of Arroyave and Gordillo are expressed per m^2. The data of Alleyne are corrected for height (m^3).

[b] Diodone clearances.

(GFR) have been well defined theoretically, but the actual regulation of filtration is not completely understood. GFR can be considered to be determined by these variables: $GFR=[K_F A]\ [(P_C-\pi)-P_T]$, where K_F is the permeability to filtration of the glomerular membrane, A is the surface area of glomerular membrane available for filtration, $(P_C-\pi)$ is the difference between glomerular hydrostatic pressure and glomerular capillary oncotic pressure, P_T is the intratubular hydrostatic pressure.

The driving force for glomerular filtration is the balance of hydrostatic and oncotic pressures acting across the glomerular membrane. In malnourished subjects mean systemic blood pressure and cardiac output are decreased [7, 20]. Consequently, glomerular hydrostatic pressure is presumably decreased. However, the marked decrease in plasma protein concentrations would decrease glomerular capillary oncotic pressure, and this in turn would tend to favor filtration.

Recent measurements of glomerular hydrostatic pressure in rats [21] indicate that the values for this parameter are actually smaller than those previously reported in the literature. Values of approximately 60 cm H_2O or 50% of mean systemic arterial pressures have been reported [22]. If the assumption is made that the mean glomerular hydrostatic pressure in humans is also approximately one-half the mean systemic arterial pressure, and if in addition it is assumed that the relationship between mean systemic blood pressure and glomerular hydrostatic pressure remains the same before and after protein repletion, certain calculations can be made regarding the forces determining glomerular filtration in a group of malnourished adults studied before and after protein repletion [15]. In these ten patients, mean systemic blood pressure rose from 81 during malnutrition to 98 mm Hg following protein repletion; at the same time plasma protein increased from 5 to 6.75 g/100 ml. If the glomerular hydrostatic pressure is 50% of mean systemic arterial pressure, its values during malnutrition and after protein repletion would be 40 and 49 mm Hg. A calculation of oncotic pressures at the level of the afferent arteriole using the expression of Landis and Pappenheimer [23] yields values of 14.8 mm Hg in the malnourished state and 30.7 mm Hg after protein repletion. This increase in glomerular oncotic pressure would exceed the calculated increase in glomerular hydrostatic pressure. Consequently, to explain the increase in GFR observed with protein repletion it must be assumed that either glomerular hydrostatic pressure increased by a value greater than that calculated from changes in mean systemic arterial pressure and/or that the relationship between glomerular hydrostatic pressure and mean systemic arterial pressure differs between the malnourished and the repleted state, the latter perhaps as the result of changes in the resistance to flow at the afferent and efferent arterioles. To our knowledge no information is available regarding values for intratubular pressure in malnutrition. Conceivably, intratubular pressure may be increased in malnutrition if reabsorption of salt and water in the proximal tubule is decreased. This will lead to increased intratubular volume and pressure, opposing filtration. Other possible factors responsible for the fall in glomerular filtration rate observed in the malnourished state may relate to a decrease in the total glomerular capillary filtering surface. Renal mass tends to decrease during malnutrition and intravenous urograms reveal an increase in renal size with protein repletion [15]. In experimental animals fed protein-deficient diets the glomeruli are actually smaller than in animals fed normal or high protein diets. These observations suggest a decrease in glomerular size and volume during malnutrition, and consequently a diminished capillary surface available for filtration. It is also possible that the hydraulic conductivity of the glomerular capillaries is altered by malnutrition and that this glomerular permeability is restored during protein repletion. However, this latter mechanism is purely speculative and no evidence is available for or against it.

Creatinine and urea clearances in malnutrition. Simultaneous measurements of inulin and creatinine clearances in subjects with protein-calorie malnutrition revealed a good agreement between the two sets of values. The mean creatinine clearance to inulin clearance ratio in seven patients was 1.06.

The clearance of urea has also been compared with the simultaneously determined inulin clearance in several subjects with protein malnutrition. Urea clearance values tended to be extremely low in these patients. Under most conditions, even in the presence of marked diuresis, the urea clearance values were 25% or lower than the simultaneously determined inulin clearance values.

It is generally recognized that the urea clearance varies with GFR and, in fact, is used clinically to approximate the latter function [24]. Urea clearance, however, is influenced by variables other than GFR. Urine flow is one of these variables and it exerts its effect by modifying the fraction of filtered urea undergoing reabsorption in the tubules. Values for urea clearances as low as 20% of contemporary GFR in the presence of high urine flows have not been reported previously in man. Chasis and Smith [25] reported a decrease in urea clearance of this magnitude in patients with glomerulonephritis. Most of these patients, however, were markedly oliguric.

A low protein intake has been noted previously to diminish the urea clearance [26]. In Longley and Miller's series it is possible to attribute this fall to a decrease in GFR. In Nielson and Bang's patients [11], however, the fall in urea clearance seemed to depend upon tubular factors entirely, since GFR did not change. Pullman et al [10] also observed in some of their normal subjects fed a low protein diet a fall in urea clearance not accountable by a change in GFR.

When the urea to inulin clearance ratios in malnourished subjects are plotted in relation to the reabsorption of water (U/P inulin ratios) it is evident (Fig. 1) that at any

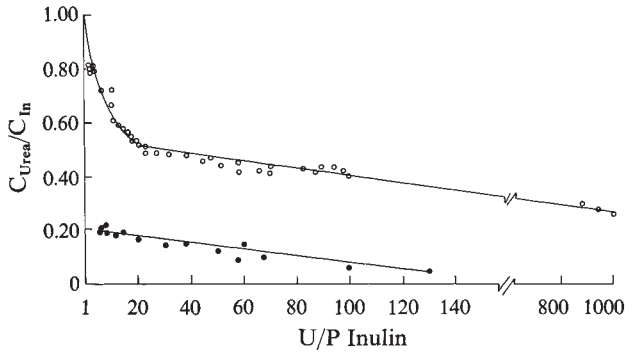

Fig. 1. *The urea to inulin clearance ratio in malnourished subjects in relation to the reabsorption of water (U/P Inulin).* The solid dots represent data in malnourished subjects. The open dots (upper curve) are from the data of Shannon (*Am J Physiol* 122: 782, 1938).

given level of fractional water reabsorption the ratio of urea to inulin clearance is markedly reduced in malnourished subjects. Indeed, some patients reabsorbed more than 90% of the filtered urea when their urine flow rate was less than 1 ml/min. Even when 16% of the filtered water was excreted (inulin U/P=6), the clearance of urea was only 20% of the inulin clearance. Unfortunately, we have no observations on urea clearance values at U/P inulin ratios below 6, since it was difficult to increase the percent of filtered water excreted above these values.

These data suggest that under conditions of protein deficiency there may be a component of active urea transport contributing to the tubular reabsorption of urea. It has been shown previously that fractional excretion of urea decreased markedly when animals were placed on a low but adequate protein diet [27, 28]. In low-protein-fed sheep and rats it was observed that the renal medullary urea concentrations were higher than urea concentrations of the final urine, indicating an active transport of urea out of the collecting duct [29]. Micropuncture experiments by Clapp [30], Lassiter, Mylle and Gottschalk [31] and Ullrich, Rumrich and Schmidt-Nielsen [32] strongly suggest that in rats fed a normal protein diet the urea transport across the collecting duct wall is passive, while in rats on a low protein diet an active outward transport is superimposed. It has been also suggested that uphill transport of urea exists in the dog and energy for this transport is derived from anaerobic glycolysis [33]. Our data, though indirect, suggest that in man, under conditions of chronic protein deficiency, an active component for urea reabsorption may be present. We have also demonstrated recently that when malnourished man is given urea a positive nitrogen balance develops, suggesting that the nitrogen of urea may be utilized in patients with severe malnutrition [34]. Similar observations have been made in malnourished children [35].

Blood urea nitrogen and plasma creatinine levels in malnutrition. Under most conditions a marked impairment in renal function can be detected by increased plasma levels of creatinine, or urea nitrogen, or both. If production of urea and creatinine is decreased, however, moderate to severe impairment of renal function might well be observed in the absence of increased plasma levels of urea nitrogen, or creatinine, or both. In patients with moderate to severe protein malnutrition, plasma levels of creatinine and urea nitrogen tend to be low despite a substantial reduction in glomerular filtration rate. Since excretion of both creatinine and urea is reduced in patients with protein-calorie malnutrition, one can conclude that the production of both of these end products is decreased in malnutrition [14]. Decreased creatinine production presumably results from a decreased muscle mass. The low urea levels probably result from decreased protein intake, decreased tissue breakdown and/or urea reutilization. During protein repletion, both BUN and plasma creatinine increase despite a concomitant increase in glomerular filtration rate. These data suggest increased entry into body fluids of both compounds during repletion. It is of interest that in children who are recovering from malnutrition urea levels may rise to values above normal. This may simply reflect the high protein intake which is usually given.

Effects of malnutrition on the renal handling of sodium. In health, the body normally maintains a relatively constant volume and composition of extracellular fluid. A large and increasing number of experimental observations now support the view that volume regulation and sodium excretion are interdependent functions. There is growing evidence that sodium mass per se is not regulated directly, nor is sodium concentration. Rather, extracellular fluid volume seems to be the sodium-related parameter of body fluids that is monitored and controlled. Thus, the sodium control system, in essence, is the volume control system.

Edema-forming states are characterized by the renal retention of salt and water. Thus, in the edema-forming syndromes, the rate of excretion of sodium and water from the body is less than the concurrent rate of acquisition. Common to all edema-forming states is the apparent need for the expansion of effective extracellular fluid volume.

Edema is not a universal finding in patients with chronic protein-calorie malnutrition. The presence or absence of edema in malnourished subjects seems to correlate well with the dietary history of salt intake in these individuals. The sodium chloride intake of the malnourished subject is extremely variable, and when easily available, salt is taken in large quantities.

Sodium balance studies performed in four nonedematous malnourished patients before and after protein repletion [36] demonstrated that on a 10 mEq salt diet, these subjects were able to decrease their urinary sodium excretion to 10 mEq or less in 24 hours. By contrast, when receiving a diet containing 170 mEq of sodium chloride, these same four patients in the malnourished state demonstrated a mean positive sodium balance of 400 mEq and weight gain of 2800 g after five days. After protein repletion the

same patients on an identical diet demonstrated a mean positive sodium balance of 150 mEq and a weight gain of 1200 g. The results of these balance studies indicate that subjects with protein malnutrition have an impaired ability to handle sodium loads when malnourished as compared to their capacity to handle the same loads after protein repletion.

We have also studied the effects of acute expansion of the extracellular fluid volume with hypotonic saline in three subjects with chronic protein malnutrition before and after protein repletion. These data are summarized in Table 2. During the malnourished state, the rapid intravenous administration of saline resulted in an almost negligible increase in fractional sodium excretion. When the same studies were repeated after protein repletion, a marked increase in fractional sodium excretion was observed.

We have also demonstrated that of the saline infused during the determination of inulin or PAH clearances, a smaller percentage was excreted in malnourished than in recovered children: in the former group, approximately 20% was excreted, there being no difference between edematous and nonedematous cases; this increased to nearly 50% in repleted children [37]. In three children with malnutrition and clinical dehydration, Gordillo et al [8] infused hypertonic saline. In only one of the children did glomerular filtration rate and effective renal plasma flow increase during the administration of hypertonic saline. Sodium diuresis did not ensue in any of the patients. A calculation of sodium balance of these three children showed that virtually all the infused sodium, and a large part of the infused water, was retained; the fact that extracellular fluid osmolality did not rise to the extent expected indicates that water moved from the intracellular compartment to the extracellular compartment and that the latter compartment presumably was expanded. Despite this, glomerular function was not restored towards normal.

The possible mechanisms responsible for the inability to handle sodium loads and the occurrence of sodium retention and edema during protein-calorie malnutrition are depicted in Fig. 2. As a consequence of a markedly decreased protein intake, there is a progressive fall in plasma albumin leading to the development of hypoalbuminemia. It is known that cardiac output is decreased in patients with chronic protein malnutrition [20]. This in turn may

Table 2. Effects of ECF volume expansion on sodium excretion in three malnourished patients before and after protein repletion

Patient		V *ml/min*	C_{In} *ml/min*	P_{Na} *mEq/liter*	$U_{Na}V$ *μEq/min*	FL_{Na} *μEq/min*	$U_{Na}V/FL$
	Before repletion						
	Control	0.61	46.3	131	43.9	5762	0.76
	Expansion	1.49	52.2	126	84.0	6248	1.34
A.V.							
	After repletion						
	Control	0.75	91.5	135	64.8	11768	0.55
	Expansion	18.8	99.3	131	1367.3	12358	11.06
	Before repletion						
	Control	0.37	38.3	125	4.8	4548	0.11
	Expansion	2.07	38.3	120	23.7	4366	0.54
F.D.							
	After repletion						
	Control	1.53	67.5	132	105	8465	1.24
	Expansion	17.7	78.1	128	1323	9497	13.93
	Before repletion						
	Control	0.35	38.8	130	30.1	4792	0.63
	Expansion	0.28	45.5	122	30.7	5273	0.58
C.V.							
	After repletion						
	Control	3.24	72.0	129	168.7	8824	1.91
	Expansion	17.7	82.5	127	817.7	9954	8.21
	Before repletion						
	Control		41.1		26.3	5034	0.50
	Expansion		45.3		46.1	5296	0.82
Mean							
	After repletion						
	Control		77.0		112.8	9686	1.23
	Expansion		86.6		1169.3	10603	11.07

V, urine flow; C_{In}, inulin clearance; P_{Na}, plasma sodium; $U_{Na}V$, sodium excretion; FL_{Na}, filtered load of sodium; $U_{Na}V/FL$, fractional sodium excretion.

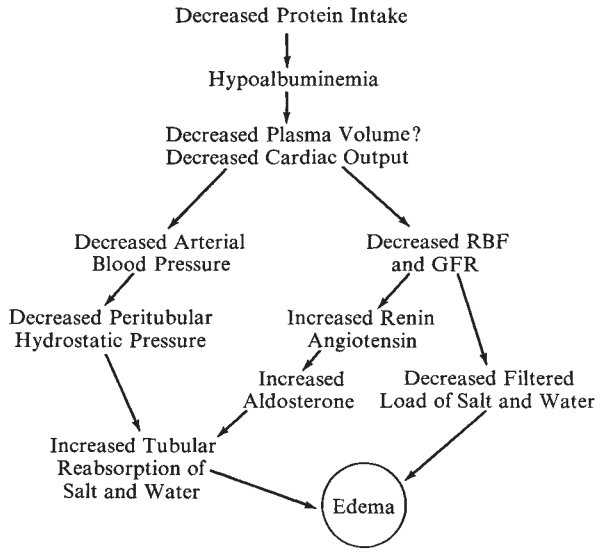

Fig. 2. *Possible mechanisms responsible for the development of edema in malnourished subjects.*

be the result of decreased plasma volume, but other factors presumably play a role [38]. Most studies suggest that both renal blood flow and GFR are decreased in chronic protein malnutrition. This is presumably the consequence of a decrease in absolute plasma volume and decreased cardiac output. A fall in GFR will markedly decrease the filtered load of salt and water. At the same time, other stimuli acting at the tubular level will tend to increase sodium reabsorption. These stimuli include: 1) elevated levels of aldosterone, presumably the result of decreased plasma volume and increased circulating levels of renin and angiotensin [39]; 2) decreased peritubular hydrostatic pressure, which presumably could result from a fall in blood pressure and cardiac output.

In patients with protein-calorie malnutrition, studies performed before and after protein repletion revealed a decrease in free water clearance values after correction of the protein deficit [36]. These data suggest that proximal sodium reabsorption may actually be decreased in the malnourished state. If so, most of the increased sodium retention ability observed in malnourished subjects could be the consequence of forces acting beyond the proximal tubule, presumably at the level of the ascending limb of Henle's loop and distal tubule. It is of interest that recently Grausz, Lieberman and Earley [40] have suggested a decreased sodium reabsorption in the proximal tubule in patients with the nephrotic syndrome. Taken together, these observations indicate that hypoalbuminemia by lowering peritubular oncotic pressure may indeed decrease proximal sodium reabsorption on a chronic basis and that the edema-forming state observed both in the nephrotic syndrome and in chronic protein malnutrition occurs despite depressed proximal tubular fractional reabsorption, and therefore may involve reabsorption of an excessively large fraction of filtered sodium in segments of the nephron located beyond the proximal tubule.

Concentration and dilution of the urine in malnutrition. The most commonly described features of renal dysfunction in malnourished patients are polyuria and nocturia. These symptoms were described in detail in World War I victims by Schittenhelm and Schelecht in 1918 [41], and since then numerous observers have confirmed the increased urine volume in the malnourished state. The usual figure for 24 hours urine volume for a semistarved subject lies between 2 and 3 liters. Klahr et al [18] studied the diluting and concentrating ability of the kidney in eight malnourished adults before and after protein repletion. Three additional patients were studied during the protein-depleted state only. A defect in renal concentrating ability was present in the 11 patients with protein malnutrition studied. Urine osmolality following 14 hours of fluid deprivation [42] never exceeded 600 mOsm/kg of water in these malnourished subjects. The concentrating defect was reversible following protein repletion in the eight patients in whom this procedure was carried out. A renal concentrating defect which improves following protein repletion has also been described in malnourished children by Alleyne [6] and by McCance, Crowne and Hall [43].

Role of antidiuretic hormone in the concentrating defect. Hormonal imbalances particularly of antidiuretic hormone have been held responsible for certain alterations of renal function in malnutrition. Since concentrated urine can be elaborated in the absence of antidiuretic hormone under conditions of decreased glomerular filtration rate per nephron [44], a phenomenon present in these patients, a lack of ADH cannot be excluded as a cause of the concentrating defect of malnutrition. Consequently, we explored the renal response of malnourished adults to the administration of Pitressin during water diuresis. After establishing adequate urine flow by the oral and intravenous administration of fluids, 15 mU of aqueous vasopressin (Pitressin, Parke, Davis and Company, Detroit, Mich.) were given intravenously. Shortly after the administration of vasopressin there was a marked decrease in urine volume and free water clearance values with a concomitant increase in urine osmolality indicating a normal response to the administration of antidiuretic hormone. However, this response to the administration of exogenous antidiuretic hormone does not exclude an abnormality in the secretion of ADH from the posterior pituitary or an abnormal response of the osmoreceptors to changes in the osmolar composition of plasma. Stimulation of the neurohypophysis by intravenous nicotine administration revealed that malnourished subjects are capable of secreting endogenous ADH. Finally, the response observed when hypertonic saline solutions were administered demonstrated the integrity of the osmoreceptors and the adequacy of the posterior pituitary gland to secrete ADH as a consequence of changes in the osmolar composition of plasma.

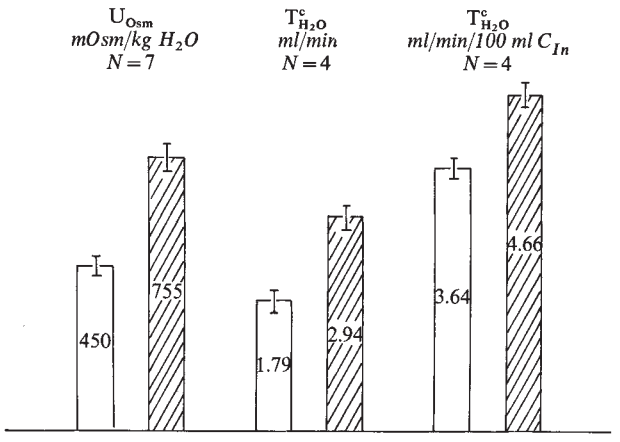

Fig. 3. *Urine osmolality and negative free water clearance in malnourished patients before (open bars) and after (striped bars) protein repletion.*

Minimal urine osmolality and free water clearance (C_{H_2O}). Data for minimal urine osmolality and free water clearance (C_{H_2O}) in seven malnourished patients revealed a mean value of 57 mOsm per kg of water for minimal urine osmolality, a figure comparable to that observed in normal subjects. Mean free water clearance values corrected for 100 ml of glomerular filtration rate was 15.8 ml, a figure also comparable to that observed in healthy subjects.

Solute free water reabsorption ($T^c_{H_2O}$). Measurements of $T^c_{H_2O}$ were obtained in four malnourished patients during mannitol diuresis and concomitant administration of vasopressin intravenously. In these patients the studies were repeated after protein repletion. The results are summarized in Fig. 3. There was a marked increase in absolute $T^c_{H_2O}$ values in all the patients studied after protein repletion. Mean $T^c_{H_2O}$ values were 1.79 ml/min before and 2.94 ml/min after correction of the protein deficit. Since GFR increased during protein repletion, values for $T^c_{H_2O}$ were corrected for 100 ml of GFR before and after protein repletion. Mean values for $T^c_{H_2O}$ for 100 ml of GFR were 3.64 ml/min in the malnourished state and 4.66 ml/min after repletion. Hence, the observed increase in $T^c_{H_2O}$ values was proportionately greater than the increase in glomerular filtration rate.

Effects of urea administration on urine osmolality. In four patients in the malnourished state urine osmolality after 14 hours of fluid deprivation was measured before and after the administration of urea orally in doses of 30 to 45 g daily. Urinary nitrogen excretion and blood urea nitrogen levels were determined daily. In every patient studied there was an increase in urine osmolality concomitant with an elevation in blood urea nitrogen levels and augmented urinary nitrogen excretion. In two patients discontinuation of urea administration resulted in a fall in the values of the three parameters studied. It has also been shown that vasopressin administration after urea loading in malnourished children resulted in increased urine osmolality.

On the nature of the concentrating defect. The improvement in the concentrating defect observed in our patients during protein repletion and the dramatic change in concentrating ability observed shortly after the administration of urea argue strongly against the possibility of an anatomic alteration as the basis for the concentrating defect in malnutrition. Rather, a functional abnormality seems to be responsible for the concentrating defect.

Impairment of sodium transport out of the loops of Henle seems unlikely since such a condition should affect both the concentrating and the diluting mechanisms. In our patients the diluting capacity was completely normal during malnutrition, indicating normal reabsorption of sodium in the ascending limbs of Henle's loops. Sodium balance studies carried out on these patients while in the malnourished state (see above) also showed adequate tubular reabsorption of sodium during periods of low salt intake.

It is now known that the formation of a hypertonic milieu in the renal medulla is responsible for the concentration of the urine. The formation of such a hypertonic milieu is thought to depend upon the active transport of sodium ions into the medullary interstitium from the fluid traversing the loops of Henle, this process occurring predominantly in the ascending limbs [45]. It is generally believed that ADH acts by increasing the permeability of the distal nephron to water, thereby permitting osmotic flow of water into the surrounding hypertonic renal interstitium. Part of the hypertonicity of the medulla is the consequence of urea accumulation, resulting from reabsorption and recirculation of this molecule. Experimental studies have shown that urea may accumulate in the interstitial fluid of the renal medulla and thereby increase the maximal osmotic pressure to which the urine can be concentrated [46]. In our patients several days to several weeks of protein repletion were usually required for improvement of the renal concentrating defect. Since in these malnourished patients positive nitrogen balance was quite marked during the first few weeks of protein repletion, urea excretion through the kidney was small initially and increased considerably only after the patients were kept for more or less prolonged periods on a high protein diet. There was a good correlation between the values for urine osmolality after fluid deprivation and the concomitant 24-hour nitrogen excretion via the kidney. These two facts strongly support the idea that decreased urea concentration in the renal medulla is reponsible for the renal concentrating defect of malnutrition. The administration of urea to these malnourished patients resulted in a marked improvement in the concentrating defect similar to the improvement seen with protein repletion. However, the response was much faster, and urine osmolality increased considerably after only four or five days of urea administration. This improvement in concentrating ability occurred pari passu with an increase in blood urea nitrogen levels. Because of the fact that urea diffuses freely across cell membranes, it is very likely that the improvement in the concentrating

defect occurred concomitantly with an increased urea concentration in the renal medulla. Again a good correlation between concentrating ability and urinary nitrogen excretion was observed. This evidence strongly supports the hypothesis that decreased urea concentration in the renal medulla is responsible for the concentrating defect present in malnutrition. Improvement in the maximal urine osmolality has been observed during the administration of urea in normal subjects receiving a low protein diet [47]. A markedly reduced concentration of urea in the renal medulla has been found in dogs fed a low protein diet, but medullary sodium concentrations have been shown to remain unchanged [48]. Crawford, Coyle and Probst [49] have clearly demonstrated that in rats placed on a low protein diet and given injections of long-acting vasopressin the administration of urea reduced urine volume further and increased urinary concentrating ability. We believe that it is possible from this data to ascribe the polyuria and the renal concentrating defect in malnutrition to decreased urea concentration in the renal medulla.

Effects of malnutrition on acid-base metabolism

Acid production. It is now well accepted that there is a dynamic equilibrium between the production and excretion of H^+. In states of renal insufficiency where there is chronic acidosis it is believed that the endogenous production of acid is not necessarily altered, but the renal mechanisms for excretion are impaired [50]. The kidney increases its output of acid under the stimulus of the acidosis produced. In the steady state, the production and excretion of acid will be evenly balanced. The endogenous production of acid, or metabolic H^+ is derived from two major sources: metabolism of dietary sulpho- and phosphoproteins and in association with organic acids. The sulphur- and phosphorus-containing amino acids are oxidized to the appropriate acids, thus promoting H^+ production.

In states of severe malnutrition, acid production is likely to be reduced. The subject when given protein will retain nitrogen, and even in the most severely malnourished children there is a strongly positive balance immediately when protein is given. Thus there will be fewer amino acids catabolized. In malnutrition there is also an adaptive change in protein metabolism [51]; in muscle there is reduced protein turnover, while in liver protein turnover is little reduced. However, there is an increase in activity of amino acid-activating enzymes of liver and a decrease in urea cycle enzymes, so that amino acids are preferentially incorporated into proteins and there is less wasteful degradation. Little is known about organic acid excretion in malnutrition; although uric acid excretion varies widely, it would be expected that when there is severe potassium deficiency, citrate excretion would be high—but this still has to be proved. We would expect that the net effect of all these adaptations would be to decrease metabolic hydrogen production.

Malnourished adults have normal blood pH and bicarbonate [52] and in malnourished children who do not have severe gastroenteritis, there is usually no evidence of metabolic acidosis. In malnourished adults, as we shall discuss later, there is a reduced acid excretion. Thus the fact that there is reduced acid excretion and a normal blood pH supports the contention that endogenous acid production is reduced in malnutrition.

Acid excretion. It is of greater importance to determine whether the malnutrition process affects the capacity of the kidney to regulate the internal environment under conditions of stress. A group of subjects were tested when they were malnourished and again after protein repletion [52]. In the malnourished state, basal net acid excretion was reduced but blood pH and bicarbonate was normal. After NH_4Cl administration there was a greater degree of acidosis in the malnourished subjects. Thus although the kidney of the malnourished adult can cope with reduced acid production, it is unable to handle an increased acid load. When the acid excretion of these subjects is further analyzed, it is clear that although the basal NH_4^+ secretion is lower, the increment after NH_4Cl administration is approximately the same in the two states; but the increment in titratable acid in the protein-repleted subjects is four times that which occurred in the malnourished.

Malnourished children given NH_4Cl do not excrete as much acid as do normal or nutritionally rehabilitated children made similarly acidotic [6]. Here again the fraction of the total acid which increases more is NH_4^+, and the fraction of the total hydrion contributed by NH_4^+ is greater in the malnourished than the well children.

Ward has compared the effects of gastroenteritis on the acid base status of malnourished and well children, and found equal degrees of acidosis in both groups [53]. This does not negate the claim that malnourished children excrete acid less well than normal children, since it is impossible to be sure in a clinical condition like gastroenteritis that the acidotic stimulus was equal in the two groups of children. It would have been interesting to know whether blood pH and bicarbonate returned to normal equally rapidly in the two sets of children.

There have been studies on a group of children who although not obviously acutely malnourished, showed evidence of growth retardation and had a mild compensated metabolic acidosis [54]. When they were given NH_4Cl, the excretion of acid was significantly lower than in children of normal stature given a comparable quantity of acid. The reduced acid excretion was reflected in both the titratable acid and NH_4^+ fractions.

Recently we have tested the ability of malnourished rats to respond to an acid load [55]. Two models of malnutrition were used. In one, rats were fed a protein-deficient diet for 21 days after weaning, thus approximating the clinical situation of childhood kwashiorkor, while "marasmic" rats were produced by having one mother suckle 16 infant rats. Neither form of malnutrition impaired the ability of

the rat to respond to NH_4Cl by an appropriate increase in urinary NH_4^+. As in malnourished adults, the basal urinary NH_4^+ of the malnourished rats was lower than that of the controls.

Urine acidification. Malnutrition does not usually impair the kidney's capacity to produce an acid urine. Smith [56] fed NH_4Cl to malnourished children and observed that urine pH did not fall as low as after they had recovered. The situation appears to be different in malnourished adults, since they could produce urine as acid as when they had recovered [52]. Similarly, in the children studied by Edelman [54], urine pH after NH_4Cl administration was the same in growth-retarded and normal children. In malnourished rats also there is no impairment of acidification [55]. It is possible that Smith's children were exceptionally malnourished or potassium-depleted, since in a later study in another group of malnourished children tested at varying times from admission through to recovery, there was no defect in urinary acidification after NH_4Cl.

The nature of the defects: a) Ammonia excretion. We have seen that in malnourished adults and rats, basal ammonia secretion is low, but under the stress of an acid load it increases appropriately. It is not a universal finding that malnutrition depresses ammonia secretion. Studies on malnourished children showed that urinary ammonia changed very little as they recovered, although ammonia as a percentage of total nitrogen decreased [57]. Adult men as well as dogs on a low protein diet do not change their ammonia excretion [58].

What is certain, however, is that malnourished adults, children and rats show a marked increase in urine ammonia when given NH_4Cl. This probably means that the intrinsic capacity of the kidney to produce ammonia is unimpaired. The source of most renal ammonia is glutamine [59] and there is no evidence that plasma glutamine falls in malnutrition. In fact, in malnourished children it is possible that glutamine may share in the rise in the plasma concentration of nonessential amino acids [60]. It has been shown that adults on a low protein diet have an increase in plasma glutamine [61]. Thus there is no lack of substrate for ammoniagenesis.

In most *in vivo* situations where there is increased renal ammonia production, as in chronic metabolic acidosis, there is also increased renal gluconeogenesis [62], and it is possible to say that the two processes may be linked without implying that gluconeogenesis is limiting in renal ammonia production. Cahill has argued however that in starved man, all the carbon liberated from amino acids in the kidney is converted to glucose [63]. It has not been possible yet to determine directly the effect of malnutrition on the gluconeogenic or ammoniagenic capacity of the human kidney. In rats however, malnutrition, although causing a decrease in basal production, does not impair the ability to increase ammonia production in response to an acid load [55]. In these same rats, there is also no impairment of the enhancement of *in vitro* gluconeogenic capacity by acidosis.

Although the relationship between gluconeogenesis and ammoniagenesis may be disputed, it is a fact that in all situations so far tested, when there is an increase in renal ammonia production *in vivo*, there is an increased activity of the enzyme of the first committed step in the gluconeogenic pathway—phosphoenolpyruvate carboxykinase (PEPCK) [64]. It has been shown that this enzyme increases in acidosis not by an increase in enzyme synthesis but because acidosis decreases the rate of enzyme degradation [65]. It is thus possible to propose the following mechanism whereby the kidney of the malnourished animal or subject might show increases in gluconeogenesis and ammoniagenesis in response to acidosis. The activity of this key enzyme PEPCK can still increase in situations in which one would expect a general decrease in protein synthesis, since with acidosis the increased activity is a function of inhibition of degradation rather than stimulation of new enzyme synthesis. Associated with this increased PEPCK, there is enhanced glutamine utilization with either ultimate formation of glucose or complete oxidation of glutamine in the TCA cycle.

Of course, it is still possible that some forms of malnutrition may cause changes in the renal tubular cell which inhibit ammoniagenic capacity. Edelman infused glutamine into his growth retarded children who had been given NH_4Cl, and although the urinary ammonia increased, it was not as high as in normal children treated similarly [54]. This would suggest some tubular cell defect. Such a study has not been made in severely malnourished children, but as pointed out before there is not likely to be any substrate lack in such children.

Even if enzymatic defects are observed in the kidneys of malnourished subjects or animals, these must be viewed with caution. For example, Kean has shown in rats that renal transaminidase, which is the enzyme involved in the first step in creatine biosynthesis, may reflect protein quality of the diet [66]; but van Pilsum pointed out that in rats on a protein-deficient diet, transaminidase activity in the kidney may fall by as much as 85% and yet body creatine and creatine phosphate remain unchanged [67].

Potassium deficiency may play a role in influencing renal excretion of ammonia in malnourished subjects. Potassium deficiency in rats leads to an increased activity of glutaminase, the enzyme which deamidates glutamine, and an increase in urinary ammonia. As pointed out above, it has been found that malnourished children have the same basal urinary ammonias as recovered children. It has also been established that most severely malnourished children are potassium-deficient [68–70]. It is thus possible that the apparently "normal" urinary ammonia of the severely malnourished children really represents increased renal production of ammonia, and the low basal urinary ammonia of malnourished adults and rats not only reflects the decreased acid load but indicates that they were not

severely potassium deficient. It would be of interest to measure urinary ammonia before and after potassium repletion in the severely malnourished children.

b) Titratable acid. In contrast with ammonia, titratable acid does not rise appropriately with acidosis. Titratable acid formation depends upon the capacity of the kidney to acidify the urine and the availability of buffers. In both malnourished adults and children, since urine acidification is not impaired, the reduced titratable acid must indicate reduced buffer availability. Waterlow and Wills show that malnourished children are phosphate deficient [71], and a low urinary excretion of phosphate is the usual finding. When phosphate was infused into three malnourished adults who were made acidotic by NH_4Cl for four days, there was the expected increase in titratable acid [52].

Effects of malnutrition on renal growth and composition

Winick and Noble [72] have shown that in the rat, growth may be divided broadly into three phases; first the phase of cell multiplication or hyperplasia; next the phase in which hyperplasia and cell enlargement or hypertrophy occur simultaneously; and the final phase in which growth occurs by hypertrophy alone. It can then be shown that dietary deprivation at different times of life followed by refeeding produces different effects. Calorie deficiency in the first or second phases of growth leads to permanent renal weight deficit, and the kidney never achieves the normal number of cells; but, on the contrary, calorie deprivation in the phase of hypertrophy alone leads to no permanent effects on kidney composition. In this context, it is important to realize the difference between the various species in the degree of maturation present at birth. In the human for example, the full nephron complement is probably present at birth; hence nutritional insults would not lead to a permanent deficit. In the rat, where kidney cellular growth and multiplication continues after birth, the situation is appropriate for producing permanent changes by dietary manipulation. When rats had both protein and calories restricted during the first 21 days of life, there was a reduction in renal cell number, whereas predominant protein restriction in the postweaning period led chiefly to a reduction in cell size. In addition, the kidney of the protein-deficient rat did not exhibit the renal hypertrophy shown by control rats in response to NH_4Cl-induced acidosis.

In Jamaica, the kidneys of children who died of malnutrition were compared with those kidneys of children dying from other causes such as accidents and acute infections. The data for American children are also given (Table 3). It is clear that especially the young malnourished children had kidneys which were smaller than those of well-nourished children. It is also interesting that the supposedly well-nourished children had kidney weights which were lower than the normal values for American children, and the difference appeared more marked with increasing age. Some electrolytes were also measured in kidneys of some other children who died of malnutrition. The values are compared with those in muscle (Table 4). Potassium and magnesium depletion were observed in muscle, but the concentration of these two cations was not greatly decreased in kidney.

Table 3. Combined kidney weights (*g*) from American children (AN), Jamaican children who died of nonnutritional causes (JN) and Jamaican children who died of malnutrition (JM)

Age (months)	AN	JN	JM
0–3	39	31	14 (1)[a]
6	48	44	18 (1)
9	61	46	25 (10)
12	67	—	43 (7)
15	71	—	34 (5)
18	81	54	53 (3)

[a] The numbers in brackets refer to the number of children examined. The data for American children were derived from Coppelletta and Wolbach [79].

Table 4. Electrolyte concentration (mEq/g N) in kidneys and muscle from eleven Jamaican children who died of malnutrition

Tissue	Magnesium	(Normal)	Potassium	(Normal)
Kidney	0.42 ± 0.07	0.50	2.0 ± 0.4	2.5
Muscle	0.33 ± 0.01	0.69	1.7 ± 0.4	3.0

The normal values are derived from WIDDOWSON EM, DICKERSON JWI: Chemical Composition of the Body in *Mineral Metabolism*, vol. II, edited by COMAR CL, BRONNER F, New York, Academic Press, 1964.

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There are few remarkable histopathological changes seen in the kidneys of malnourished children who die. Bras, Waterlow and DePass [73] reported swelling of the capsular epithelial cells and occasional hyalinization of a whole or part of the glomerulus and deposition of fine eosinophilic granular material in cells. These changes were not specific, occurring as often in children who died from causes unrelated to malnutrition. However, a later study from the same laboratory showed that 22 of 31 infants who died of malnutrition had significant renal histological lesions [74]. Cortical calcification was present in some cases and others had nonspecific tubular lesions. An unsuccessful attempt was made to correlate the post mortem renal histology with levels of various electrolytes in serum obtained before death. A study of renal biopsies from malnourished children has shown that there may be minor glomerular and tubular changes which can persist even after nutritional recovery [75].

In rats acute starvation leads to a dramatic fall in kidney protein content [76], but in pigs chronic undernutrition does not produce any remarkable change in the kidney weight/body weight ratio and there is little change in the

gross composition [77]. An interesting phenomenon was described by Bras and Ross on rats [78]. These workers observed that there was an age-associated kidney disease in the rat, which they described as "progressive glomerular nephrosis" characterized by gradually increasing density of the glomerular intercapillary structures, thickening of the basement membrane and ultimate glomerular sclerosis. Rats which were restricted in their intakes of protein, carbohydrates or calories showed a most striking reduction in this kidney disease. It appeared that carbohydrate or calorie restriction was more beneficial than protein restriction. Thus far there has been no claim of a reduction in any form of human chronic renal disease in those parts of the world where calorie and protein undernutrition are endemic.

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